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Part III: Clinical Departments and Divisions --- Chapter 10: Division of Hematology (pages 284-297)

CHAPTER TEN

Division of Hematology

ALLAN J. ERSLEV, M.D.

"The blood is the life."

—DEUTERONOMY 12:23

IN THE early part of this century medicine began to change from an art to a science, from observation and palliation to testing and treatment. This change was associated with an increasing demand for doctors to be informed and experienced in the management of all illnesses, and it became more and more difficult to live up to the Oslerian tradition of being a complete general physician. The field was too great; many physicians began to restrict their study to certain diseases and became recognized not for their breadth of knowledge but rather for their narrow competence in the malfunction of a single organ. At Jefferson, John Chalmers DaCosta, Jr., a cousin of John Chalmers DaCosta, the Gross Professor of Surgery, was the first American physician to write a textbook on hematology (Figure 10-1). This textbook, entitled *Clinical Hematology,* was first published in 1901 and predated Wintrobe's famous textbook of the same name by 41 years. A second edition appeared in 1905 and was used in the teaching of medical students during their rotation in the newly created Laboratory of Clinical Medicine. This laboratory, first installed in the Jefferson Medical College Annex building on Tenth Street, was then considered one of the first and most advanced developments in the use of a laboratory for medical teaching. It was directed in turn by Doctors Erwin D. Funk, Henry Mohler, and Harold Jones, but it was under Dr. Jones' leadership that it first became hematologically oriented.

Early Hematology at Jefferson

Dr. Harold W. Jones (1891–1959), after graduation from Jefferson in 1917, served as a Lieutenant in the Army Medical Corp at Fort Oglethorpe. From 1919 to 1921 he was Chief Resident physician at Jefferson (Figure 10-2). He practiced for a while as a general internist, but after being put in charge of the Laboratory of Clinical Medicine his interest turned to disorders of the blood. One of the main functions of the course in Laboratory Medicine then as now was to teach medical students how to examine and observe blood, but he realized that there was very little clinical or pathophysiologic follow-up. He suggested to Dr. Thomas McCrae, the Magee Professor of the Principles and Practice of Medicine, that Jefferson should establish what we now would designate as the Division of Hematology. Specifically, he suggested the development of three facilities: one for the accurate study of patients with blood disorders by specially trained technical and professional personnel; one consisting of laboratories for the long-term study of fundamental aspects of blood diseases; and one for a facility to provide transfusions of carefully matched blood.

The present Division of Hematology was an outgrowth of these early ideas, but until 1939 no organizational facility could be established because of lack of funds. Nevertheless, Dr. Jones proceeded with independent and unfunded studies of blood diseases and blood transfusions. He

published widely and wrote a number of textbook articles dealing with the problems of anemia, hemorrhagic disorders, and the direct and indirect transfusion of blood.[1] Jones was one of the founders of the Jefferson Society for Clinical Investigation at his alma mater. Nationally, he was known as an outstanding physician and hematologist, was elected to fellowship in the American College of Physicians, and was made a member of the Association of American Physicians and the Interurban Club.

CLINICAL

HEMATOLOGY

A PRACTICAL GUIDE

TO THE

EXAMINATION OF THE BLOOD WITH

REFERENCE TO DIAGNOSIS

BY

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1901

FIG. 10-1. First American textbook of hematology (1901), by John Chalmers DaCosta, Jr., M.D.

■ Leandro M. Tocantins (1901–1963)

In his work and hematologic interests Jones was supported by Dr. Leandro M. Tocantins (1901–1963), a young Brazilian-born physician who graduated from Jefferson Medical College in the Class of 1926 after a classic premedical education abroad and at Cornell University (Figure 10-3). He interned at Chestnut Hill Hospital and then practiced general medicine for three years in Cleveland, Ohio. Tocantins returned to Jefferson and became a J. Ewing Mears Research Teaching Fellow until 1936, after which he received a faculty appointment. Dr. Tocantins early became involved in the study of hemostasis and blood coagulation, but his interests were, like those of Dr. Jones, directed at all aspects of hematology. He published widely on such diverse subjects as anti-platelet serum, urine anti-thromboplastin, bone marrow infusions, lipid anticoagulants, and abnormal hemoglobins. As a special student of bleeding disorders, his name became linked to the effect of inhibitors of blood coagulation and especially the hypothesis that hemophilia is caused

FIG. 10-2. Harold W. Jones, M.D. (1891–1959).

by such inhibitors. His work on blood platelets resulted in the classic monograph *Mammalian Blood Platelets in Health and Disease,* published in 1938, which exerted a major influence on subsequent studies of this blood component.[2] Tocantins also spearheaded the field of autoimmunity by infusing an anti-platelet serum and producing thrombocytopenia. This study led to attempts to treat both idiopathic thrombocytopenic purpura and acquired hemolytic anemia with macrophage blocking agents such as radioactive gold.

These were years in which investigators provided for their own livelihood through busy medical practice and squeezed research into spare hours and free weekends. The new Magee Professor of Medicine, Dr. Hobart A. Reimann, was keenly aware of that and hoped for a day when investigators could be released from the burden of full-time practice and devote a major part of their time to scientific investigation within their special fields. Dr. Reimann was also a strong supporter of Dr. Jones' effort to develop a Division of Hematology, but funds were needed to fulfill these dreams. It was not until 1939, when Mr. and Mrs. Thomas D. Cardeza became interested in the project, that substantial backing was obtained for the development of a research-oriented Division of Hematology.

FIG. 10-3. Leandro M. Tocantins, M.D. (1901–1963).

The Cardeza Foundation

Mr. Thomas Drake Martinez Cardeza (1875–1952) was the last scion of the Drake family, which came to the United States from Leeds, England in 1828 (Figure 10-4). His ancestors Thomas Drake (1807–1890) and his brother moved to Philadelphia from Ohio in 1837 and established a small woolen mill in Manayunk. They began to manufacture jeans under the trade name of "Kentucky Jeans." Their business prospered with the establishment of

FIG. 10-4. Thomas Drake Martinez Cardeza (1875–1952).

additional mills near the present South Street Bridge and at Twenty-first and Pine Streets. With the heavy demand for woolens by the Union Army, further expansion took place, and at the end of the Civil War Thomas Drake retired a wealthy man. He was highly respected in the business community and was able to augment his fortune with successful investments in real estate. He held a number of trusteeships and was an organizer and director of the old Fidelity Trust Company, a position he held until his death in 1890. With his wife Matilda and seven children, Mr. Drake lived the style of the very rich. In his large estate in Germantown he had a small zoo, with free-roaming elks and bison, and kennels for Great Dane dogs. Sadly, six of his seven children died at a young age, many from scarlet fever, leaving Charlotte Drake (1854–1939) as the sole heiress to his fortune.

In 1874, Charlotte married James Warburton Martinez Cardeza, the grandson of Count Juan Martinez Cardeza, a nobleman from La Coruna, Spain. However, after her only son Thomas was born, she divorced and from then on devoted her life to her son and to the sports and pleasures of the leisure class (Figure 10-5). She and Thomas circumnavigated the globe on her steam ocean-going yacht, *The Eleanor*, with its crew of 39 and guest rooms for 16 (Figure 10-6). As an ardent and accomplished hunter she pursued big game in India and Africa. She and Thomas maintained a hunting lodge at Moose Head Lake in Maine, a shooting establishment in Montana, and a hunting Schloss in Austria. She was also a patron of the opera and of the Academy of Music, and was a witty and beautiful lady of high society in Philadelphia. In 1912, she and Thomas were on the *Titanic* together but both survived (Figure 10-7). All kinds of rumors were circulated afterwards about how Thomas had gotten into a lifeboat, rumors that undoubtedly made his survival difficult to enjoy.

From all accounts, it appears that Charlotte ran the family with a firm hand. When Thomas married Mary Racine (1880–1943), another determined woman (Figure 10-8), he was caught between two strong-willed ladies separated by background and religion. Mary was born in France and was a Roman Catholic. They were married in secret, and the conversion of Thomas to Catholicism was difficult for Charlotte to accept. However, both families lived in estates not far apart in Germantown and together they maintained the zoo and kennel established by Thomas Drake.

After World War I, Mary developed a chronic incapacitating illness, the nature of which is unknown, but it led her into a close personal and professional relationship with Dr. Harold Jones at Jefferson. He became a close friend of the family and treated Mrs. Cardeza both at home and in Jefferson hospital with a variety of medications, including direct infusions of small amounts of whole blood obtained from a donor at the bedside. He talked to them about his dream of establishing a transfusion and hematology research center at Jefferson. When Charlotte Drake Cardeza died in 1939, Thomas and Mary decided to support the development of such a center in her memory.

FIG. 10-5. Mrs. Charlotte Drake Cardeza (1854–1939).

On December 14, 1939, at a memorable dinner at the University Club, attended by Mr. Cardeza and many department heads, Dr. Jones toasted the establishment of a Hematology Division in the Department of Medicine (Figure 10-9), to be named The Charlotte Drake Cardeza Foundation for the Study of Diseases of the Blood and Allied Conditions. After two years of legal and academic discussions between Mr. J. Harry Wagner, legal counsel for the Cardezas, and Mr. Robert P. Hooper, President of the Board of Trustees of Jefferson, the Charlotte Drake Cardeza Foundation was formally incorporated on October 17, 1941, to be directed by Dr. Harold Jones, as the first Thomas Drake Martinez Cardeza Professor of Clinical Medicine and Hematology in the Department of Medicine (Figure 10-10). Jones was allotted a teaching service in the Department of Medicine, plus adult and pediatric hematology beds in the Hospital. Staff members for the Division of Hematology and a number of research and teaching Charlotte Drake Cardeza Fellows were recruited. The Division was to conduct and operate a Transfusion-Plasma Unit and a Biologic Photographic Unit, activities to be supported by an annual grant from the Cardezas of $50,000 for not less than ten years, $7,500 of which could be used for the salary of the Director of the Division of Hematology.

Although the Charlotte Drake Cardeza

FIG. 10-6. Charlotte and Thomas Drake Cardeza on board *The Eleanor*.

Foundation served as the Division of Hematology of the Department of Medicine, the Director reported to a Cardeza Foundation Advisory Committee of the faculty appointed by the Board of Trustees, rather than to the Chairman of the Department of Medicine. The Committee in turn reported to the Board of Trustees. Subsequent changes in the line of command provided for two channels, one academic, via the Chairman of the Department of Medicine, and one fiscal, via a Cardeza Foundation Faculty Advisory Committee to a Joint Advisory Committee comprised of appropriate individuals representing the Board of Trustees, administration, faculty, and the Cardeza Trust.

Mr. Cardeza was the first Chairman of the Joint Advisory Committee, and until 1947 he had almost daily administrative contacts with Dr. Jones. At that point, he requested that Jefferson Medical College take over supervision of activities of the Foundation and changed the annual allotment of $50,000 to a corresponding amount derived from a Trust deposited at the Fidelity Bank. Mr. Horace Liversidge became Chairman, and Mr. Percival Foerderer and Mr. J. Harry Wagner were two of the more active committee members. With the additional support of a legacy of about $100,000 from the Kress brothers, considerable research was carried out in laboratories spread throughout the College.

In two small laboratories in the College Building and one in Room 247 in the Thompson Annex, Dr. Franklin A. Miller (Figure 10-11), who had been recruited as Assistant Director, and Dr. Leandro Tocantins, Co-Assistant Director, had for that period a great opportunity to pursue their research interest almost full-time. Dr. Miller's interest was in the pathogenesis of malignant lymphomas and leukemias. He succeeded in isolating from the urine of patients with these illnesses several substances that when injected into guinea pigs would alter cellular proliferation.

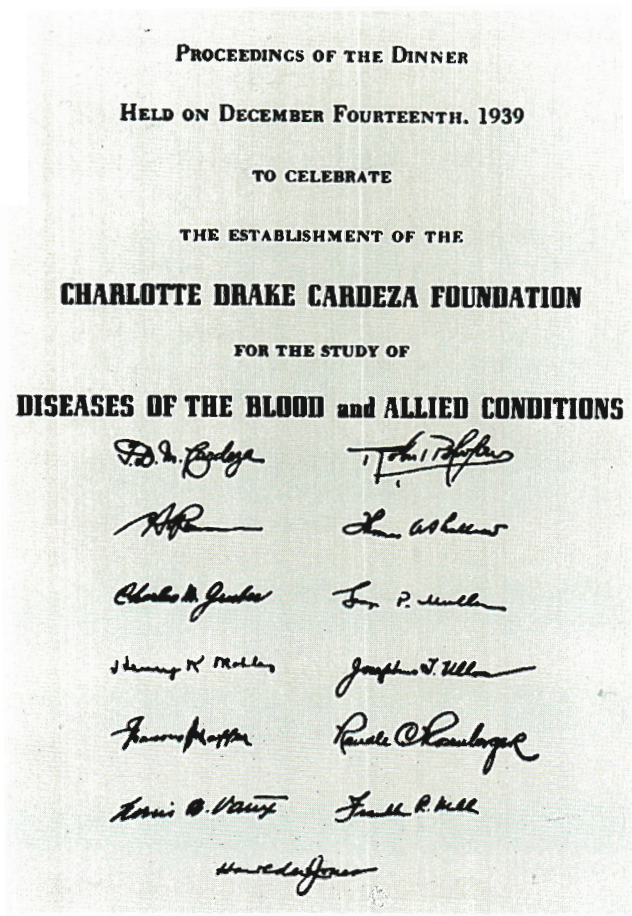
FIG. 10-7. Cabin door hardware and receipts of the Cardeza passage on the *Titanic*.

FIG. 10-8. Mary Racine (1880–1943).

Dr. Daniel Turner (Figure 10-12), an organic chemist, characterized these substances, and in many papers they hypothesized regarding their possible pathogenetic relationship to malignancy. Dr. Tocantins continued his work on platelets and the coagulation inhibitor found in some patients with hemophilia, and with Dr. Robert Carroll (Jefferson, 1952) and Dr. Ruth Holburn (Figure 10-13) he established a Hemophilia Clinic. Dr. Jones was primarily involved in patient management centered around a clinic in the Curtis Building designated the Blood, Spleen, and Bone Marrow Clinic. With Dr. Lowell A. Erf, Jones also established a Blood Bank in a small building on Eleventh Street and became deeply involved in the processing and administration of plasma.

In 1952, Mr. Cardeza died and left his estate for the support of The Charlotte Drake Cardeza Foundation. After some years of intense legal wrangling, his mansion in Germantown was bequeathed to the Archdiocese of Philadelphia, and his fortune, about $3 million, was used to establish a trust for the Foundation with Mr. Wagner and the Fidelity Bank as co-trustees. This input of funds permitted the recruitment of more staff members. When Dr. Tocantins became the new vigorous Director in 1954, he spearheaded further expansion. Dr. Tocantins and Dr. Farid I. Haurani (Figure 10-14) began studies on bone marrow transplantation. After both exciting and painful experiences they learned that although autotransplantation was possible, still unknown immunologic barriers prevented successful heterotransplantation.[3] With the help of Dr. Louis A. Kazal (Figure 10-15), Dr. Daniel Turner, and Dr. Melvin J. Silver (Figure 10-16), Dr. Tocantins continued his quest for the identification of the elusive inhibitor that he believed characterized hemophilia.[4] That quest was actually not finished until Dr. Sandor S. Shapiro (Figure 10-17), after the death of Dr. Tocantins, identified the inhibitor as a Factor VIII antibody that develops in about ten to 15 percent of treated patients with hemophilia.[5]

In 1959 Dr. Allan J. Erslev was recruited from the Thorndike Memorial Laboratory at Harvard as Associate Director. He pursued his work on erythropoietin, a renal hormone he had discovered earlier. This hormone controls the rate of red cell production and plays a major role in recovery from blood loss and in adaptation to high altitudes.[6]


PROCEEDINGS OF THE DINNER

HELD ON DECEMBER FOURTEENTH, 1939

TO CELEBRATE

THE ESTABLISHMENT OF THE

CHARLOTTE DRAKE CARDEZA FOUNDATION

FOR THE STUDY OF

DISEASES OF THE BLOOD and ALLIED CONDITIONS

FIG. 10-9. Dinner proceedings at the establishment of Charlotte Drake Cardeza Foundation.

The Sansom Street Center

The trust income was, according to Mr. Wagner, restricted to support personnel and provide supplies and equipment and could not be used for renovation. Fortunately, a new chairman of the Joint Advisory Committee, Mr. J. Howard Pew, President of Sun Oil Company, saw the need for providing a separate building for the Foundation, and through his generosity a three-storied property on 1015 Sansom Street was purchased and completely renovated (Figure 10-18). In 1960, the

Foundation moved in and for the first time became a coherent unit, permitting easy academic and personal interaction among its members. The move was followed by an expansion in personnel and activities, an expansion greatly enhanced by the new availability of federal research funds. In a few years, federal grant support actually matched and exceeded trust income. The new Cardeza quarters housed the Blood Donor Center, a photographic unit, and laboratories and offices for a professional staff that had increased to include 15 M.D.'s and Ph.D.'s, five to ten American and foreign clinical and Research Fellows, and a nonprofessional staff of about 60 technicians, secretaries, and maintenance personnel.

Academically, the Foundation was primarily the Division of Hematology in the Department of Medicine, but it also served as the Division of Hematology in the Departments of Pediatrics, Physiology, and Pharmacology. It was responsible for the teaching of hematology to students and house staff, and clinically its members provided consultations and care for hematologic patients in the Jefferson Medical College Hospital.

In 1963, after Dr. Tocantins' sudden death, Dr. Allan J. Erslev (Figure 10-19), a native of Denmark (born in 1919), became Director. He continued the recruitment of new investigators and expansion of federal funding. Dr. Sandor Shapiro (Figure 10-17), the first senior recruit, was trained at Harvard and Massachusetts Institute of Technology; after arrival at Cardeza he established

FIG. 10-10. Harold W Jones, M.D. and his Cardeza Staff.

a Thrombosis and Hemorrhagic Disease Section and a state-supported Hemophilia Center.

With Drs. Melvin Silver, Louis Kazal, Jose Martinez (Figure 10-20), and J. Bryan Smith (Figure 10-16), Shapiro spearheaded research in coagulation-factor kinetics, the immunologic basis for some coagulation disorders, and the biochemical processes involved in platelet aggregation and release action.[7–11] Dr. Edward Burka, Dr. Elias Schwartz, Director of the Division of Pediatric Hematology, and Miss Jean Atwater (Figure 10-21), Head of Cardeza Laboratories, studied normal and abnormal hemoglobins and identified the defects responsible for several hemoglobinopathies and thalassemias.[12,13] Their laboratories served as a

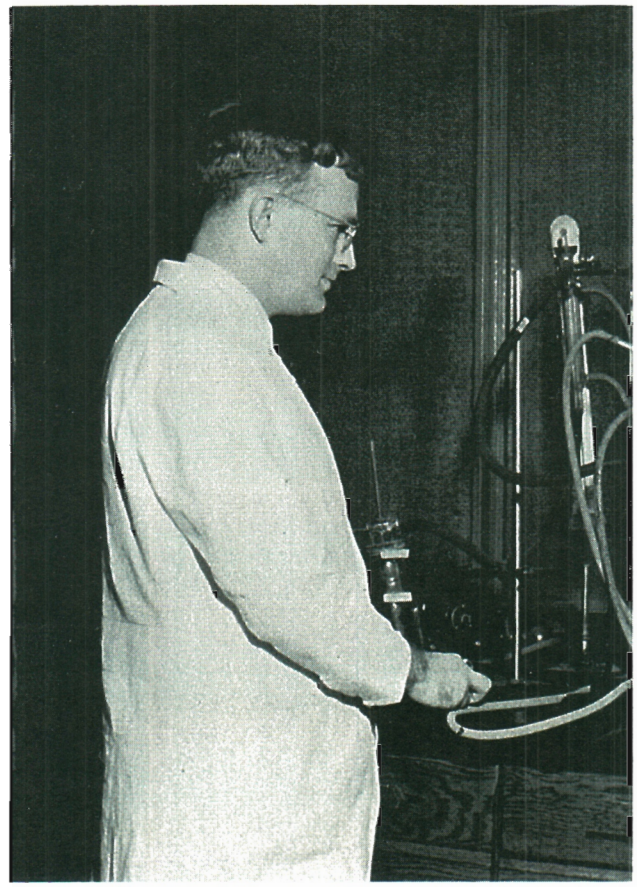


FIG. 10-12. Daniel Turner, Ph.D.

FIG. 10-11. Franklin R. Miller, M.D.

FIG. 10-13. Ruth Holburn, Ph.D.

nationally recognized referral center for abnormal hemoglobins. Dr. Burka also established a state-supported Sickle Cell Center and became Blood Bank Director. These positions were later taken by Dr. Samir K. Ballas, with the assistance of Dr. Stephen P. Hauptman for tissue typing and Dr. Scott Murphy (Figure 10-22) for blood fractionation. Dr. Ballas' interest was directed mainly at the red cell membrane with its external antigenic sites and internal structural skeleton,[14] while Dr. Hauptman studied the same membrane structures on lymphocytes.[15] Dr. Murphy's primary interest was platelets, and he established storage conditions for platelets that effectively increased their shelf life from hours to the present seven days.[16] Dr. Susan Travis, who followed Dr. Schwartz as Director of Pediatric Hematology

FIG. 10-15 Mr Orin Miller (technician to Louis Kazal for 30 years), Louis A. Kazal, Ph.D., and Sandor Shapiro, M.D.

FIG. 10-14 Farid I Hauram, M D

FIG. 10-16. Melvin J Silver, D.Sc., and J Bryan Smith, Ph.D

was primarily involved in unraveling red cell enzyme function.[17] Dr. Haurani's interest centered on iron and B_{12} metabolism. He directed the Jefferson branch of the National Cooperative Acute Leukemia Group B (ALGB). Dr. Erslev continued his research in erythropoietin with Dr. Thomas Gabuzda, Dr. Ruth Silver, and Dr. Lewis Kazal. Later, Dr. Jaime Caro joined his team and provided further information about the renal biogenesis and bone marrow action of this hormone.[18] They also established a research and referral center for erythropoietin bioassays and for the diagnosis of polycythemia vera, secondary polycythemia, and the anemia of chronic renal disease.

Concomitantly with these research activities, all clinical members of the Cardeza Foundation were members of the Cardeza Associates of Clinical Hematology and shared in consultations at the Thomas Jefferson University Hospital. With the competent support of some outstanding nurses, (Marian Ramp and Kay Houser are excellent examples), they provided in- and outpatient management of patients with hematologic

FIG. 10-18. The Cardeza Foundation at 1015 Sansom Street.

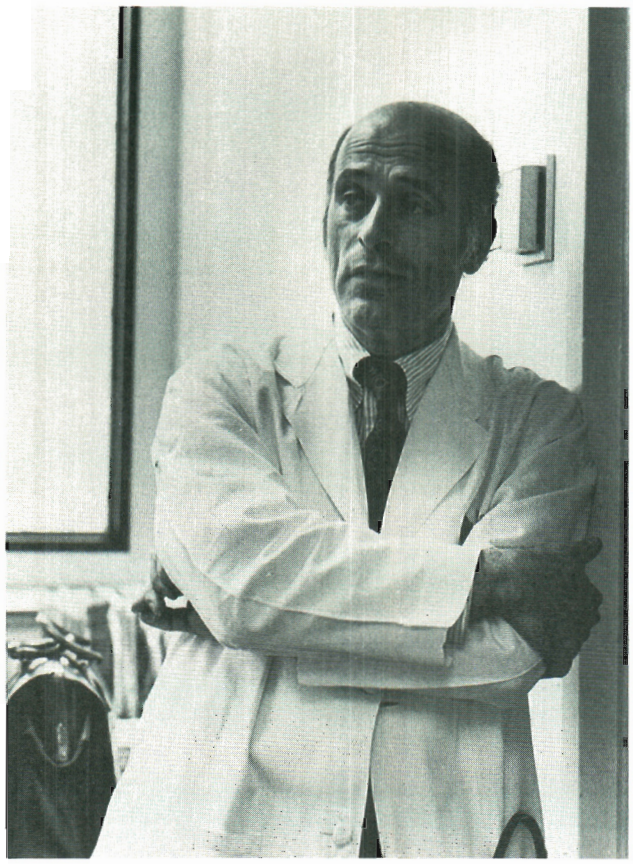


FIG. 10-17. Sandor S. Shapiro, M.D.

FIG. 10-19. Allan J. Erslev, M.D. (1919–).

disorders. Assisted by the more clinically oriented faculty members, Drs. John Hodges and Edward McGehee, they also taught hematology to Jefferson students and house staff and provided clinical and research instruction to Fellows supported by two National Institutes of Health Training Grants.

Numerous reviews and textbook articles resulted. Dr. Erslev became coeditor of a major textbook, *Hematology*,[19] and, with Dr. Gabuzda, coauthor of a small paperback *Pathophysiology of Blood*.[20] Both books have gone through three editions.

FIG. 10-20. Jose Martinez, M.D.

FIG. 10-21. Jean Atwater.

In 1975, the Cardeza building had to make room for the new Thomas Jefferson University Hospital. The foundation moved into 1,600 square feet of a completely renovated laboratory and office space on the seventh, eighth, and ninth floors of the

FIG. 10-22. Scott Murphy, M.D.

Curtis Building (Figure 10-23). The Cardeza Blood Donor Center and Tissue Typing Center as well as the Sickle Center moved into the first floor and the Cardeza Hemophilia Unit into the second floor of the old hospital, and the outpatient facilities were located eventually on the fourth floor of the New Hospital. The move into new laboratories symbolized the move in research from the days of traditional morphologic and pathophysiologic studies to the current phase of molecular biology. Studies became characterized by monoclonal antibodies, restriction enzyme analysis, radioimmune assays, membrane receptor analysis, cell sorting, and gene cloning. Young investigators such as Drs. Perumal Thiagarajan, Carol Ingerman-Wojenski, Patricia Catalano, Iftekhar Alam, and Jaime Caro adopted these new techniques and turned research efforts at Cardeza in that direction. Although the funding never seemed to match expenditures, the annual Cardeza budget was maintained in precarious balance by the competent juggling of the administrative assistants, Bella Sigal and Helen Gilliam. In 1984–1985, the budget reached about $3.5 million, with $2.3 million provided from federal grants and contracts.

In 1985 Dr. Erslev stepped down as Director of the Division but remained at Jefferson to continue his research on red cell diseases. He was immediately named Distinguished Professor of Medicine, the first in the Department of Medicine to be so honored. Previous awards included a Guggenheim Fellowship, presentation of his portrait by the Class of 1972, and the first

FIG. 10-23. Hematology conference room and Leandro M. Tocantins Library on the ninth floor of the Curtis Building (1975).

William B. Castle Lectureship at Boston University. He remained prominent in many of the important clinical and research societies related to his field both here and abroad.

The Division may look back with pride to its contributions to the understanding and treatment of diseases of the blood and look forward under the new leadership of Dr. Sandor Shapiro to the challenge of a future in hematologic molecular biology.

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